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Adaptive Parameter Modulation of Deep Brain Stimulation in a Computational Model of Basal Ganglia-thalamic network

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Abstract

Deep brain stimulation (DBS) has proven to be an effective treatment for Parkinson's disease (PD). Adaptive control strategies offer the potential to improve efficacy, limit side effects and save battery consumption via reducing the total amount of stimulation delivered. However, the mechanisms underlying the beneficial effects of DBS for PD remain poorly understood and are still under debate, which has hindered the development of closed-loop DBS. And during the chronically implanted phase, adaptive DBS needs to be further improved to maintain its advantages. In the design of new adaptive DBS, more insights into inaccuracies when establishing mathematical basal ganglia model, unknown external disturbance signal and dynamics of focal area should be considered. A controlled auto-regressive moving average is used as the representative description of stimulus-response relationship based on recursive extended least square method, where stimulation signal is applied to subthalamic nucleus (STN) and the feedback signal is selected as local field potential signal from globus pallidus (GPi). The generalized minimum variance algorithm is used for online update of stimulation frequency and amplitude in a closed-loop manner. Simulation results illustrated the efficiency of the proposed closed-loop stimulation methods in disrupting the aberrant beta band oscillation and restore normal firing pattern when compared with the PD state. Robustness of the adaptive algorithm was further verified through dynamic change of illness state.

Keywords: Deep brain stimulation; Basal ganglia; Mathematical Model; Input-Output identification; Generalized minimum variance algorithm

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder associated with the degeneration of dopaminergic neurons in the substantia nigra par compacta [1]–[6]. Up till now, more than ten million people are suffering from the motor symptoms such as bradykinesia, rigidity, rest tremor, and postural and gait impairment worldwide [7], [8]. Conventional deep brain stimulation (DBS) has significantly improved the treatment of PD through continuously delivering high frequency electrical stimulation to specific subcortical targets, including the subthalamic nucleus (STN) and the internal segment of the globus pallidus (GPi) [9]–[13]. However, its open-loop mode induces limitation on side-effects, battery-consumption and parameter-programming, which presents demands for a more automated and intelligent approach [14]–[19].

In recent years, closed-loop stimulation that utilizing patients' clinical states as a guide to alter stimulation parameters as necessary has attracted more attention [20]–[27]. It provides an effective approach to optimize clinical benefits whilst minimizing side effects and battery depletion. A critical step in the development of such systems is the identification of signal features or “biomarkers” which have the potential to quantify clinical states [28], [29]. To date, local field potentials (LFPs) have become a commonly adopted feedback signal for closing the loop due to its correlation to patients' clinical states and the ease with which they can be acquired [26], [30]–[32]. Little et al. adopted an “on-off” pattern to deliver the stimulation signals, which indicates that the stimulator is on only when the detected LFPs beta amplitude exceeds certain threshold [22]. Although this adaptive DBS was shown to be at least as effective as conventional DBS, and stimulation time and side effects were reduced, but from a chronically implanted phase its stun effect will disappear. Thus, new adaptive DBS directs to modulate the stimulation parameters based on new algorithm is required. Proportional control strategy has also shown potential in computational studies but restricted due to the time-consuming parameter adjustment process [33]. While it largely depended on the properties of controlled brain network, which left still a long way from clinical implementation. However, the precise mathematical model of the

Parkinsonian focal area could not be established [34]. Besides, individual variation and illness progress need further to be characterized to guarantee precise stimulus mode [35]–[37]. The above two points put forwards exacting requirements for the development of closed-loop strategy. To address the problem, a self-tuning controller, which combines the recursive method of parameter estimation and different types of control algorithms, is proposed to form a real-time computer control system, thereby realizing the adaptive adjustment of parameters (including frequency and amplitude) of DBS signal. Considering the inherent time delay between excitatory or inhibitory neurotransmitter transmission between populations within Basal Ganglia-Thalamus (BG-Th) model, it is necessary to predict the control effect in advance of this time delay so as to avoid suboptimal control effect [38]–[40]. With the advantage of simple in algorithm and easy to implement, minimum variance control has become the foundation of other self-tuning control algorithms [41], which could be utilized in our work to develop a predictive closed-loop system. The rest of the paper is organized as follows. In Section II, models and methods are introduced. Firstly, introduction of the computational model and selection of feedback signal were given, so as to generate input-output data for the identification of the stimulus-response relationship. Then, the control framework was described in detail. Computer simulation results were presented in Section III. Finally, the discussion and conclusion were given in Section IV.

2. Methods

In this section, we started by describing a previously proposed mathematical model of Parkinsonian focal zone, which was adopted here as the data generator and stimulation testbed. Considering that Parkinsonian behaviors were related to rhythmic firing patterns with oscillations at beta band [29], the relationship between the applied stimulus signal and the LFPs output was established through real-time online identification, based on which the closed-loop controller was developed and designed for selection of optimal stimulation to improve Parkinsonian state as shown in Fig. 2.

2.1 Model description

The biological plausible mathematical BG-Th model that presented by So et al. [42] was modified from classical Rubin-Terman model [43]. Compared with the original Rubin-Terman model, the change of ionic current types and the network topological structure prompted the firing properties better match experimental data. Therefore, it was an excellent platform to study effects of neural activation or silencing and to test the adaptive control algorithm in this paper.

The BG-Th network was formed by excitatory or inhibitory synaptic connections among four primary nuclei including STN, GPe, GPi and Th. Each STN neuron received inhibitory connections from two GPe neurons. Each GP (GPe and GPi) neuron received excitatory inputs from two STN neurons and inhibitory inputs from two GPe neurons. Each Th neuron received inhibitory input from one GPi neuron. All connections that following a structured and deterministic pattern were illustrated in Fig. 1. The number of cells in each nucleus was 10, which was proven to be sufficient to generate same trends of normal and Parkinsonian states when compared with larger number of cells in each population. The single compartment Hodgkin–Huxley type equations were used to describe firing dynamics of STN, GPe, GPi and Th

$$\begin{aligned}
 C_m \frac{dv_{STN}}{dt} &= -I_l - I_{Na} - I_K - I_T - I_{Ca} - I_{AHP} - I_{GPe \rightarrow STN} + I_{app_STN} + (I_{DBS}) \\
 C_m \frac{dv_{GPe}}{dt} &= -I_l - I_{Na} - I_K - I_T - I_{Ca} - I_{AHP} + I_{STN \rightarrow GPe} - I_{GPe \rightarrow GPe} + I_{app_GPe} \\
 C_m \frac{dv_{GPi}}{dt} &= -I_l - I_{Na} - I_K - I_T - I_{Ca} - I_{AHP} + I_{STN \rightarrow GPi} - I_{GPe \rightarrow GPi} + I_{app_GPi} \\
 C_m \frac{dv_{Th}}{dt} &= -I_l - I_{Na} - I_K - I_T - I_{GPi \rightarrow Th} + I_C
 \end{aligned} \tag{1}$$

where $C_m = 1 \mu F/cm^2$ was the membrane capacitance, $v_i (i \in STN, GPe, GPi)$

represented the membrane potential. On the right side of equation,

$I_l, I_{Na}, I_K, I_T, I_{Ca}, I_{AHP}$ were respectively the leak current, the sodium current, the potassium current, the low-threshold calcium current, the high-threshold calcium current and the after hyper polarization potassium current.

$I_{app_i} (i \in STN, GPe, GPi)$ represented constant positive bias current that input from unmodeled brain regions, such as striatum. The transition from normal state

to Parkinsonian states was modeled by changing the value of $I_{app_i} \cdot pd = 0$ represented the normal state and $pd = 1$ represented the PD state, thus we got the following relationship

$$\begin{cases} I_{app_STN} = 33 - 10 * pd \\ I_{app_GPe} = 20 - 13 * pd \\ I_{app_GPi} = 21 - 6 * pd \end{cases} \quad (2)$$

Besides, $I_{\alpha \rightarrow \beta} (\alpha, \beta \in \text{STN, GPe, GPi})$ described the synaptic connections from pre-synaptic nucleus α to post-synaptic nucleus β ,

$$I_{\alpha \rightarrow \beta} = g_{\alpha \rightarrow \beta} (v_{\beta} - E_{\alpha \rightarrow \beta}) \sum_j s_{\alpha}^j, \quad (3)$$

where $g_{\alpha \rightarrow \beta}$ and $E_{\alpha \rightarrow \beta}$ represented the maximal synaptic conductance and reversal potential respectively, and $\sum_j s_{\alpha}^j$ was the sum of synaptic variables. In addition to ionic currents and synaptic currents, for Th neurons, I_c denoted a series of excitatory current pulses from cortical neurons and followed a gamma distribution with the average rate of 14 Hz and the variation of 0.2, the amplitude and pulse duration of which were set to $3.5 \mu\text{A}/\text{cm}^2$ and 5 ms respectively. Moreover, the implementation of DBS stimulus took the form as

$$I_{\text{DBS}} = A_{\text{DBS}} H\left(\sin \frac{2\pi t}{\rho_{\text{DBS}}}\right) \cdot [1 - H(\sin(2\pi t + \delta_{\text{DBS}}) / \rho_{\text{DBS}})] \quad (4)$$

Conventional effective stimulus parameters were usually set to be

$A_{\text{DBS}} = 300 \mu\text{A}/\text{cm}^2$, $\delta_{\text{DBS}} = 0.3 \text{ ms}$ and $\rho_{\text{DBS}} = 7.69 \text{ ms}$ (130 Hz). While in this paper, values of DBS parameters were modulated based on real-time calculation from closed-loop controller.

For the case of frequency modulation,

$$\rho_{\text{DBS}} = 1000 / u(k) (f_{\min} \leq u(k) \leq f_{\max}) \quad (5)$$

For the case of amplitude modulation,

$$A_{\text{DBS}} = u(k) (A_{\min} \leq u(k) \leq A_{\max}) \quad (6)$$

where $f_{\max}$ and $f_{\min}$ were the maximum and minimum bounds of the modulated DBS frequency, $A_{\max}$ and $A_{\min}$ were the maximum and minimum bounds of the modulated DBS amplitude, and calculation of $u(k)$ was introduced in the following part. Details of equations and parameters were given in Table 1, where membrane potentials, synaptic conductance, currents were expressed in mV , mS/cm^2 and $\mu A/cm^2$ respectively. Simulations were implemented in Matlab R2019a (The Math Works, Natick, MA), and the equations were solved using the forward Euler method with a time step of 0.01 ms.

2.2 Identification of the stimulus-response relationship

PD was a progressive neurodegenerative disease. Selection of appropriate biomarker to capture ongoing clinical changes was a critical process. It has been proved that beta-band oscillation of LFPs signals was related to motor symptoms of bradykinesia and rigidity across patients. Recent research presented the evidence that LFPs signals that directly recorded from DBS electrodes appear to be a promising source of feedback signal. Based on the mathematical BG-Th network, the LFPs signal of GPi nucleus [44] could be computed by

$$LFP_{GPi} = I_{STN \rightarrow GPi} - I_{GPe \rightarrow GPi} + I_{app_GPi}, \quad (7)$$

which was approximated by the sum of transmembrane currents.

However, due to the characteristic of highly nonlinearity within BG-Th network, it presented huge challenges in the design of closed-loop control algorithm. A recursive extended least square (RELS) method was proposed to realize online real-time parameter estimation, therein the model structure could be delineated by the controlled auto-regressive moving average (CARMA) model

$$A(z^{-1})y(k) = z^{-d}B(z^{-1})u(k) + C(z^{-1})\xi(k) \quad (8)$$

where $u(k)$ represented the input DBS stimulus signal (to STN), $y(k)$ represented the output LFPs signal (from GPi) at time kT_s ($T_s=0.01ms$ was the sampling interval), $\xi(k)$ was Gaussian white noise series that representing the sum of the stochastic perturbation and unmodeled dynamics. and d was the time delay. Coefficients of polynomial

$$\begin{cases} A(z^{-1}) = 1 + a_1 z^{-1} + a_2 z^{-2} + \dots + a_{n_a} z^{-n_a} \\ B(z^{-1}) = b_0 + b_1 z^{-1} + b_2 z^{-2} + \dots + b_{n_b} z^{-n_b} \\ C(z^{-1}) = 1 + c_1 z^{-1} + c_2 z^{-2} + \dots + c_{n_c} z^{-n_c} \end{cases} \quad (9)$$

were to be determined by detectable input and output data.

Firstly, the CARMA model was written in least squares form

$$y(k) = \boldsymbol{\varphi}^T(k) \boldsymbol{\theta} + \xi(k) \quad (10)$$

where

$$\begin{cases} \boldsymbol{\varphi}(k) = [-y(k-1), \dots, -y(k-n_a), u(k-d), \\ \dots, u(k-d-n_b), \xi(k-1), \dots, \xi(k-n_c)]^T \\ \boldsymbol{\theta} = [a_1, \dots, a_{n_a}, b_0, \dots, b_{n_b}, c_1, \dots, c_{n_c}]. \end{cases} \quad (11)$$

Due to the uncertainty of $\xi(k)$ in $\boldsymbol{\varphi}(k)$, it was substituted using the estimation value $\hat{\xi}(k) = y(k) - \hat{y}(k) = y(k) - \hat{\boldsymbol{\varphi}}^T(k) \boldsymbol{\theta}$. Then, least squares estimation was performed to minimize the performance evaluation

$$J = \sum \varepsilon^2(k) = \sum [y(k) - \hat{\boldsymbol{\varphi}}^T(k) \boldsymbol{\theta}]^2 \quad (12)$$

If we took the derivative of J with respect to $\hat{\boldsymbol{\theta}}$ (let it equal to 0), then continuously revised the latest estimation parameter $\hat{\boldsymbol{\theta}}(k)$ based on last $\hat{\boldsymbol{\theta}}(k-1)$ and correction term, it could be derived that

$$\begin{cases} \hat{\boldsymbol{\theta}}(k) = \hat{\boldsymbol{\theta}}(k-1) + \mathbf{K}(k)[y(k) - \hat{\boldsymbol{\varphi}}^T(k) \hat{\boldsymbol{\theta}}(k-1)] \\ \mathbf{K}(k) = \frac{\mathbf{P}(k-1) \hat{\boldsymbol{\varphi}}(k)}{1 + \hat{\boldsymbol{\varphi}}^T(k) \mathbf{P}(k-1) \hat{\boldsymbol{\varphi}}(k)} \\ \mathbf{P}(k) = [\mathbf{I} - \mathbf{K}(k) \hat{\boldsymbol{\varphi}}^T(k)] \mathbf{P}(k-1) \end{cases} \quad (13)$$

2.3 Controller design

To automatically adjust DBS parameters, a real-time computer control system was established by combing the recursive method of parameter estimation and self-tuning control method. Considering the existence of time lag between DBS action and LFPs output, the generalized minimum variance control (GMVC) predicted the output in advance, and then designed the control law to guarantee the stability of BG-Th network [45].

According to the CARMA model of Eq. (10),

$$y(k+d) = \frac{B(z^{-1})}{A(z^{-1})}u(k) + \frac{C(z^{-1})}{A(z^{-1})}\xi(k+d) \quad (14)$$

since that $\xi(k+1), \dots, \xi(k+d)$ could not be acquired at time kT_s , $\frac{C(z^{-1})}{A(z^{-1})}$ was

divided into two parts based on observability and unobservability

$$\begin{cases} F(z^{-1}) = 1 + f_1 z^{-1} + \dots + f_{d-1} z^{-(d-1)} \\ G(z^{-1}) = g_0 + g_1 z^{-1} + \dots + g_{n_a-1} z^{-(n_a-1)} \end{cases} \quad (15)$$

Therefore,

$$\frac{C(z^{-1})}{A(z^{-1})} = F(z^{-1}) + \frac{z^{-d}G(z^{-1})}{A(z^{-1})} \quad (16)$$

Combined with $\xi(k) = \frac{A(z^{-1})}{C(z^{-1})}y(k) - \frac{B(z^{-1})}{C(z^{-1})}z^{-d}u(k)$, it could be obtained that

$$y(k+d) = F(z^{-1})\xi(k+d) + \frac{B(z^{-1})F(z^{-1})}{C(z^{-1})}u(k) + \frac{G(z^{-1})}{C(z^{-1})}y(k) \quad (17)$$

In view that $\xi(k+d)$ was independent of $\{y(k), y(k-1), \dots, u(k), u(k-1), \dots\}$, the optimal least variance prediction was

$$y^*(k+d) = \hat{y}(k+d) = \frac{B(z^{-1})F(z^{-1})}{C(z^{-1})}u(k) + \frac{G(z^{-1})}{C(z^{-1})}y(k) \quad (18)$$

$$y(k+d) = F(z^{-1})\xi(k+d) + y^*(k+d) \quad (19)$$

Further, to improve closed-loop system performance, to soften the desired output and to constraint on control input, weighted polynomial $P(z^{-1})$, $R(z^{-1})$ and $Q(z^{-1})$ were introduced

$$\begin{cases} P(z^{-1}) = 1 + p_1 z^{-1} + p_2 z^{-2} + \dots + p_{n_p} z^{-n_p} \\ R(z^{-1}) = 1 + r_1 z^{-1} + r_2 z^{-2} + \dots + r_{n_r} z^{-n_r} \\ Q(z^{-1}) = 1 + q_1 z^{-1} + q_2 z^{-2} + \dots + q_{n_q} z^{-n_q} \end{cases} \quad (20)$$

By this time, the cost function was expressed in

$$\begin{aligned}
C &= E \left\{ \left[P(z^{-1})y(k+d) - R(z^{-1})y_r(k+d) \right]^2 \right\} + \left[Q(z^{-1})u(k) \right]^2 \\
&= E \left\{ \left[PF\xi(k+d) + Py^*(k+d) - Ry_r(k+d) \right]^2 \right\} + \left[Qu(k) \right]^2
\end{aligned} \tag{21}$$

The first term was omitted due to its independence with past input and output, then we took the partial derivative of rest terms in Eq. (21) with respect to $u(k)$

$$2 \left[Py^*(k+d) - Ry_r(k+d) \right] \frac{\partial Py^*(k+d)}{\partial u(k)} + 2 \left[Qu(k) \right] \frac{\partial Qu(k)}{\partial u(k)} = 0 \tag{22}$$

Substituting $\frac{\partial Py^*(k+d)}{\partial u(k)} = b_0$, $\frac{\partial Qu(k)}{\partial u(k)} = q_0$ into Eq. (22),

$$\left[Py^*(k+d) - Ry_r(k+d) \right] * b_0 + Qu(k) * q_0 = 0 \tag{23}$$

the generalized minimum variance control law was obtained as

$$u(k) = \frac{Ry_r(k+d) - GPy(k)}{\frac{q_0}{b_0}CQ + BFP}, \tag{24}$$

where the control signal at time kt_s was obtained to be applied to the BG-Th model target.

3. Results

3.1 Simulated BG-Th network firing pattern

The transition from normal state to Parkinsonian state was achieved by changing the level of bias currents to STN, GPe and GPi neurons. As shown in Fig. 3 (a), (b) and (c), the STN, GPe and GPi neurons exhibited regular spiking in the normal physiological condition. While in the PD state, a rhythmic bursting fashion occurred, especially in the GPe and GPi neurons as shown in Fig. 3 (d), (e) and (f). Then, we measured the relay ability of Th neurons in the reference of cortex input. Error index

$$EI = \frac{N_{error}}{N_c} \tag{25}$$

was defined as a valid proxy to quantify the reliability of Th neurons. When the transmembrane voltage crossed the threshold of -40mV, a spike of Th neuron was

detected. Correspondingly, an error was defined when a spike failure occurred in response to cortex input. N_{error} represented the total number of errors (including missing spikes, rebound bursts and spurious events) in thalamic transmission, and N_c summed the number of cortex input pulses. As shown in Fig. 4, more firing errors occurred due to rhythmic pattern of GPi neurons in the pathological condition, with the error index EI increased from 0.0073 (normal condition) to 0.4365 (PD condition). Besides, GPi LFPs that approximated by the sum of transmembrane currents were presented in Fig. 5, power spectral analysis of which manifested a beta-band oscillation under PD condition, when compared with normal condition.

3.2 Performance of stimulus-response identification

A CARMA model was identified to establish the relationship between DBS stimulation signal and the LFPs response signal. Based on the obtained input and output data from the BG-Th network, it was necessary to select appropriate order parameters by quantifying the estimation accuracy. Since parameters $[c_1, c_2, \dots, c_{n_c}]$ were used to measure the influence of uncertain dynamics, n_c was set to 3. The root mean square error

$$e = \sqrt{\frac{1}{N} \sum_{n=1}^k (y(k) - \hat{y}(k))^2} \quad (26)$$

between actual value and estimated value of LFPs signal in GPi was calculated and compared among different model structures. As shown in Fig. 6 (a), it was found that identified error was always smaller than 0.95 and simultaneously it decreased with the increase of n_a and n_b . But to reduce computational complexity n_a and n_b were all set to 4. In this case, evolution of estimation results was illustrated in Fig. 6 (b), where all identified parameters rapidly converged to stable values. Correspondingly, the identification performance was exhibited in Fig. 6 (c), where the red solid line displayed the original data that recorded from BG-Th network output and the blue dotted line represented the estimated data generated from CARMA model. The result suggested that the CARMA model provided a good fit to the obtained input-output data.

3.3 Efficacy of GMVC strategy

The design of closed-loop DBS system was based on the identified parameters of the CARMA model, with the frequency or amplitude calculated based on the adaptive generalized minimum variance controller. For the case when DBS was applied to STN neurons with real-time frequency modulation since $t=1000$ ms, rhythmic bursting firing pattern of GPi was obviously suppressed as denoted by comparison of LFPs waveform signal before and after stimulation as shown in Fig. 7 (a). Fig. 7 (b) indicated the change of stimulation frequency by the sparse and intensive distribution stimulus pulse, where $f_{\max}$ and $f_{\min}$ were set to 200 Hz and 50 Hz to simulate clinically effective frequency bands. As shown in Fig. 7 (c), quantitative analysis through power spectrum indicated the disrupted pathological frequency structure after closed-loop DBS amplitude modulation. Similarly, for the case when DBS was applied to STN neurons with real-time amplitude modulation, suppression of rhythmic oscillated firing pattern and disruption of pathological spectrum structure were realized since $t=1000$ ms as shown in Fig. 8.

Further analysis of closed-loop performance was developed in terms of interspike interval (ISI) changes as shown in Fig. 9, where abscissa presented ISI distribution and ordinate empirical cumulative distribution function. Regular spike firing in normal condition was always accompanied by uniform distribution of small ISI, while burst firing pattern was accompanied by dispersion of ISI. Specifically, as shown in Fig. 9, ISI distributed mainly around 20 ms in normal state. In PD state, distribution of ISI focused around 10 ms and 60 ms, which represented the strong polarization that induced by increase of pathological burst firing. As the stimulus signal was applied, the pathological condition of ISI distribution was gradually recovered with the tendency towards normal distribution, under both closed-loop frequency modulation and amplitude modulation.

As described ahead, the Parkinsonian state was simulated by decreasing the constant bias currents that applied to the STN, GPe and GPi neurons. Directly switching I_{app_i} from a higher value to a lower value apparently ignored the possible intermediate states resulting from diverse courses of disease caused by individual differences, thus we defined a dynamic parameter pd to quantify

disease severity. Correspondingly, the robustness and adaptability of GMVC strategy on closed-loop control performance was tested by continuously changing pd from 0 to 1. Wherein, the approximate integration of spectral power corresponding to 12-35 Hz was calculated as a Beta index to distinguish normal state from PD state. As shown in Fig. 10, the red error bar presented the trend of Beta index with the increase of pd . Real-time closed-loop frequency modulation and amplitude modulation was implemented as pd increased from 0.1 to 1. In both cases, the increased Beta index was almost pulled back to normal state as denoted by grey error bar with yellow round markers and grey error bar with green square markers, indicating the restoration of the spectral features.

4. Discussion and conclusion

The objective of this study was to design a closed-loop control strategy to suppress Parkinsonian state. To advance the progress of neurophysiological experiments, reveal the principles of information processing and various functions of the nervous system, we focused on the model research to inspire new treatments for neurological disorders. In this paper, the computational BG-Th network that consisting of STN, GPe, GPi and Th neurons was constructed based on Hodgkin–Huxley type equation, where parameter settings and synaptic connections were formed obeying anatomy and physiological properties. Based on the findings that the rhythmically oscillatory activity of LFPs is a remarkable PD-related feature, LFPs of GPi neurons was considered as a feedback signal that distinguish normal condition from PD condition. Due to the lack of adequate physiological details and uncertainties in noise or disturbances, a black-box model approach based on the CARMA model was utilized to remedy above limitation, where the mathematical model generated data was input to the black box. Therefore, it was expected to describe the relationship between stimulation signal and neuronal response according to the identification method. Then adaptive reprogramming DBS stimulation parameters in reducing the adverse effects of continuous high-frequency DBS was tested through the proposed self-tuning control strategy GMVC.

Numerical simulation results illustrated the possibility of mitigating intractable Parkinsonism by GMVC, including the suppression of abnormally enhanced beta band oscillation and the regulation of interspike interval distribution. Firstly, the

intrinsic transmission time delay between STN and GPi cannot be neglected, which was considered in the design of the closed-loop system. Secondly, to overcome model limitation caused by symptom severity, it was hypothesized to represent possible dynamics by adjusting the parameter pd from 0 to 1, and the GMVC strategy reached remarkably excellent controlling performance. Although robustness of the proposed control algorithm was tested based on data extracted from a modified computational model from Rubin-Terman model, it was still far from enough to reveal the real brain network and inevitably ignore considerable physiological knowledge. Therefore, the potential application of GMVC in future clinical DBS will consider much more issues, such as which is the most appropriate biomarker to be the feedback variable and how they vary across patients and time, which of or what combination of the parameters (amplitude, frequency, or pulse width) is the best beneficial. Further verification of this method in other computational models and animal experiments was expected in future work.

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Conflict of Interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in.

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Figure Legends

Fig. 1. BG-Th network model. (a) indicated the network layout and (b) depicted details of synaptic connections among STN, GPe, GPi and Th nucleus within the network, where red arrows denote excitatory connections and black arrows denote inhibitory connections.

Fig.2 The diagram of CARMA model-based generalized minimum variance control system

Fig. 3 Firing rastergrams of STN, GPe and GPi neurons under normal ((a), (b) and (c)) condition and PD ((d), (e) and (f)) condition.

Fig. 4. Membrane potential traces of the Th neurons. Orange pulse trains denoted excitatory cortex input signals, blue traces in upper and bottom panels represented the normal condition (a) and the PD condition (b), respectively.

Fig. 5. The LFPs signal of GPi under (a) normal ($pd = 0$) and (b) PD ($pd = 1$) conditions. (c) exhibited the power spectrum distribution within 0-50 Hz in normal state and PD state.

Fig. 6. (a), (b) and (c) displayed the estimation process of model parameters and (d) explicated the identification result of LFP_{GPi} under the input of square-wave DBS signal (with the frequency of 130 Hz).

Fig. 7. Frequency modulation based on GMVC strategy. (a) was evolution of the LFP_{GPI} where external stimulation was exerted since $t=1000$ ms. (b) Waveform of the stimulation signal I_{DBS} that calculated according to the GMVC strategy. (c) Comparison of the power spectral analysis before and after the external stimulation. Weighted polynomial P, R and Q were set to 1, 1 and 0.001 respectively, and d was set to 5.

Fig. 8. Amplitude Modulation based on GMVC strategy. (a) was evolution of the LFP_{GPI} where external stimulation was exerted since $t=1000$ ms. (b) Waveform of the stimulation signal I_{DBS} that calculated according to the GMVC strategy. (c) Comparison of the power spectral analysis

before and after the external stimulation. Controller parameters were set the same as the case of frequency modulation.

Fig. 9. Empirical cumulative distribution function of Interspike interval (ISI) distribution under normal, PD, PD condition with closed-loop frequency modulation and PD condition with closed-loop amplitude modulation.

Fig. 10. Control performance of (a) frequency modulation (b) amplitude modulation under different Parkinsonian states. Standard error bars were shown for 10 simulations for each value of pd .

Table 1 Equations and parameters of the STN, GPe, GPi and Th neurons

	STN	GPe(GPi)	Th
Ionic currents			
I_L	$2.25(v+60)$	$0.1(v+65)$	$0.05(v+70)$
I_K	$45n^4(v+80)$	$30n^4(v+80)$	$5(0.75(1-h))(v+75)$
I_{Na}	$37m_\infty(v)^3 h(v-55)$	$120m_\infty(v)^3 h(v-55)$	$3m_\infty(v)^3 h(v-50)$
I_T	$0.5a_\infty(v)^3 b_\infty(r)^2 v$	$0.5a_\infty(v)^3 rv$	$5p_\infty(v)^2 rv$
I_{Ca}	$2c^2(v-140)$	$0.15s_\infty(v)^2(v-120)$	--
I_{AHP}	$20(v+80)([Ca]/([Ca]+15))$	$10(v+80)([Ca]/([Ca]+10))$	--
Gating kinetics			
n_∞	$\frac{1}{1+\exp((-v-32)/8)}$	$\frac{1}{1+\exp((-v-50)/14)}$	--
m_∞	$\frac{1}{1+\exp((-v-30)/15)}$	$\frac{1}{1+\exp((-v-37)/10)}$	$\frac{1}{1+\exp((-v-37)/7)}$
h_∞	$\frac{1}{1+\exp((v+39)/3.1)}$	$\frac{1}{1+\exp((v+58)/12)}$	$\frac{1}{1+\exp((v+41)/4)}$
a_∞	$\frac{1}{1+\exp((-v-63)/7.8)}$	$\frac{1}{1+\exp((-v-57)/2)}$	--
b_∞	$\frac{1}{1+\exp((-r+0.4)/0.1)} - \frac{1}{1+\exp(4)}$	--	--
r_∞	$\frac{1}{1+\exp((v+67)/2)}$	--	$\frac{1}{1+\exp((v+84)/4)}$
c_∞	$1/(1+\exp((-v-20)/8))$	--	--
s_∞	--	$\frac{1}{1+\exp((-v-35)/2)}$	--
p_∞	--	--	$\frac{1}{1+\exp((-v-60)/6.2)}$
τ_n	$1 + \frac{100}{1+\exp((v-80)/26)}$	$0.05 + \frac{0.27}{1+\exp((v-40)/12)}$	--
τ_h	$1 + \frac{500}{1+\exp((v-57)/3)}$	$0.05 + \frac{0.27}{1+\exp((v-40)/12)}$	$\frac{1}{1+\exp((v+41)/4)}$
τ_r	$7.1 + \frac{17.5}{1+\exp((v-68)/2.2)}$	--	$\frac{0.15}{28+\exp((-v-25)/10.5)}$
τ_c	$1 + \frac{10}{1+\exp((v+80)/26)}$	--	--

Figures

Figure 1

BG-Th network model. (a) indicated the network layout and (b) depicted details of synaptic connections among STN, GPe, GPi and Th nucleus within the network, where red arrows denote excitatory connections and black arrows denote inhibitory connections.

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Frequency modulation based on GMVC strategy. (a) was evolution of the LFP_{GPI} where external stimulation was exerted since $t=1000$ ms. (b) Waveform of the stimulation signal DBS I that calculated according to the GMVC strategy. (c) Comparison of the power spectral analysis before and after the external stimulation. Weighted polynomial P, R and Q were set to 1, 1 and 0.001 respectively, and d was set to 5.

Figure 8

Amplitude Modulation based on GMVC strategy. (a) was evolution of the LFP_{GPi} where external stimulation was exerted since $t=1000$ ms. (b) Waveform of the stimulation signal DBS I that calculated according to the GMVC strategy. (c) Comparison of the power spectral analysis 22 before and after the external stimulation. Controller parameters were set the same as the case of frequency modulation.

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